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AST-120 (Spherical Carbon Adsorbent) in the Treatment of Perianal Fistulae in Mild-to-Moderate Crohn's Disease: FFAST-1, a Phase 3, Multicenter, Placebo-controlled Study

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Abstract

Background—AST-120 (spherical carbon adsorbent) was previously reported to be effective for perianal fistula healing in Japanese patients with mild-to-moderate Crohn's disease.

Methods—To evaluate the efficacy and safety of AST-120 in a Western population, a phase 3, multicenter, randomized, double-blind, placebo-controlled, study (FFAST-1) was conducted in adult patients with at least 1 draining perianal fistula and a Crohn's disease activity index <400. Patients received either AST-120 or matching placebo at a dose of 2 g 3 times daily for 8 weeks. The primary endpoint was the proportion of patients with treatment success, defined as a 50% reduction in the number of draining fistulae, at both weeks 4 and 8. A multivariate model was generated to assess covariates for treatment success among baseline variables.

Results—Two hundred forty-nine patients were randomized (AST-120; n = 122; placebo, n = 127). The proportions of patients achieving the primary endpoint were no different between treatment groups (13.9% versus 16.5%, $P = 0.6$). No differences in fistula response were noted at week 4 (23.0% versus 25.2%, $P = 0.77$) or week 8 (27.0 versus 34.6%, $P = 0.22$). Serum C-reactive protein concentrations >0.6 mg/dL and Crohn's disease activity index scores >151 at baseline were associated with a reduced likelihood of treatment success (odds ratio, 0.40; confidence interval, 0.19–0.87; $P = 0.02$; and odds ratio, 0.45; confidence interval, 0.21–0.97; $P = 0.04$, respectively).

Conclusions—In this largest placebo-controlled trial to date to evaluate the impact of a therapeutic agent on perianal fistulae in Crohn's disease, the efficacy of AST-120 could not be

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S. Hanauer, S. Travis, and M. S. Harris have previously served as consultants to Ocera Therapeutics. M. S. Harris owns stock in Ocera Therapeutics and was an employee during the time this study was conducted. The remaining authors have no conflicts of interest to disclose.

The original protocol is available from Ocera Therapeutics on request.

confirmed. An inverse relationship was observed between both inflammatory and clinical disease activity and fistula response.

Keywords

Crohn's disease; fistula; perianal disease; AST-120; spherical carbon adsorbent

Perianal fistulizing disease occurs in up to 40% of patients with Crohn's disease¹⁻³ and impairs quality of life.^{4,5} Antibiotics⁶⁻⁸ and immunosuppressive agents^{8,9} have been used with some success, but many of these trials were small, inconclusive, confounded by concomitant treatments, or fistula healing represented only a secondary trial endpoint.¹⁰ Prospective studies have demonstrated that anti-tumor necrosis factor (TNF) agents can promote fistula closure¹¹ and maintain healing in a portion of patients.^{10,12} However, safety concerns, including development of resistance because of use of broad-spectrum antibiotics or opportunistic infections associated with immunosuppressives or anti-TNF- α agents, highlight the need for alternative treatments.

AST-120 (spherical carbon adsorbent) is an orally ingested agent that is comprised of porous, spherical carbon particles of 0.2 to 0.4 mm in diameter with high adsorption ability and extensive surface area (1600 m²/g). The agent has been used in Japan since 1991 (Kremezin; Kureha Corporation, Tokyo, Japan) for the treatment of patients with chronic kidney disease.¹³ The clinical utility of AST-120 is thought to reside in its ability to adsorb small molecular weight toxins, inflammatory mediators, and bile acid products from the gastrointestinal (GI) tract, preventing local toxicity and their systemic absorption.¹⁴⁻¹⁶ AST-120 has a selective adsorption profile for certain acidic and basic organic compounds and has a lower adsorptive capacity than activated charcoal for digestive enzymes. The prolonged kinetics of adsorption (5-7 h) results in a pharmaceutical substance with predominantly lower GI tract effects and reduced interaction with nutrient and drug-absorbing surfaces proximally. AST-120 is not absorbed after ingestion, and its safety profile has been established in over 360,000 patients with chronic kidney disease in Japan over the past 2 decades.

The ability of AST-120 to improve fistulae associated with Crohn's disease was first observed in patients with concomitant chronic kidney disease. Subsequently, Fukuda et al¹⁷ reported the beneficial effects of AST-120 from a randomized, double-blind, placebo-controlled trial of 62 Japanese patients with mild-to-moderate Crohn's disease and draining perianal fistulae. A significantly higher proportion of patients reported a reduction of 50% or more in the number of draining fistulae with AST-120 as compared with placebo after both 4 and 8 weeks of treatment. The Perianal Disease Activity Index (PDAI) and Crohn's Disease Activity Index (CDAI) improved accordingly.

The purpose of this trial (FHASt-1) was to broaden this preliminary experience to a larger group of Western patients with perianal fistulizing Crohn's disease. The trial results were used to evaluate the demographic and disease factors underlying fistula closure in these patients.

MATERIALS AND METHODS

Study Population

Male and female patients between 18 and 70 years of age with a documented diagnosis of Crohn's disease including ileitis, colitis, or ileocolitis, and at least 1 draining perianal fistula, along with a CDAI¹⁸ score of less than 400, were eligible to participate in the trial. Patients with enterocutaneous and rectovaginal fistulae were eligible for enrollment if they had at least 1 perianal fistula. Concurrent therapies for Crohn's disease, including aminosalicylates, antibiotics, and immunosuppressives were permitted provided they were stable for at least 2, 4, and 12 weeks, respectively, before enrollment and remained constant during treatment. Concomitant corticosteroid therapy was also permitted provided the patient was on a stable dose (20 mg/d of prednisone or equivalent) for at least 4 weeks. Investigators were permitted to make corticosteroid dosage adjustments during the course of the trial provided the dosage did not increase above the baseline dose. Patients were allowed prior use of anti-TNF α and other biological immunosuppressive agents provided there was a documented prior response to therapy (defined as a 50% reduction from baseline in the number of fistulae over at least 4 weeks), and the agent was discontinued at least 3 months before randomization. Antidiarrheal medications were permitted but restricted to loperamide and diphenoxylate.

Patients were excluded because of any of the following reasons: presence of an entero-entero, rectovesical, or enterovesical fistula; symptomatic strictures or clinical obstruction; surgical ileostomy; short bowel syndrome; total parenteral nutrition as the sole source of nutrition; hemoglobin <8.5 (female patients) or 10.0 g/dL (male patients); platelet count below 100,000/mL; and severe diarrhea, defined as >10 liquid bowel movements per day. Patients were also excluded for local complications of fistulizing disease, including abscesses, for which surgery might more appropriately be indicated. Setons, when present, were excluded unless removed at least 48 hours before randomization.

Study Medication

AST-120 (spherical carbon adsorbent; Kureha Corporation) and matching placebo (Celphere 305; stained to match the appearance of AST-120) were supplied in aluminum-covered mylar sachets, each containing 2 g of study medication. Patients were instructed to take study medication 3 times daily at least 30 minutes after eating and 30 minutes before or after concomitant medications. They were instructed to tear the sachet, pour the sachet contents onto the backs of their tongues, and to swallow the contents with 8 ounce of water.

Study Design

This was a multi-center, prospective, double-blinded, randomized, placebo-controlled, parallel group, 2-armed study conducted at 89 sites in the United States, Canada, Europe, and Israel from March 2006 to March 2008.

Patients entered a 14-day screening period to establish baseline assessments (Fig. 1). Eligible patients were randomly assigned to receive blinded treatment with either AST-120 or matching placebo 2 g 3 times daily for 8 weeks. Patients who did not respond after

completing the first full course (8 wk) of randomized treatment had the option to receive the alternate blinded treatment (AST-120 to placebo or placebo to AST-120) for 1 treatment course. Responders were followed monthly to the time of relapse or week 24, whichever occurred sooner.

Patients were declared treatment failures and terminated from study participation if they developed an abscess or symptomatic stricture, need for any surgical intervention for Crohn's disease, an increase in CDAI score by 70 points above baseline, or above a total score of 400, or if they required administration of any additional therapies or dose increases of concomitant medications (including corticosteroids) for Crohn's disease. Patients who did not respond or continued to worsen could be discontinued at the discretion of the investigator.

The randomization schedule was generated using SAS software (SAS Institute Inc., Cary, NC) using a blocked randomization scheme and a block size of 2. Study drug was randomly assigned to subjects in sequential subject number order. The study was kept blinded to all operational personnel through completion of study conduct.

Efficacy and Safety Evaluations

The primary efficacy assessment, the number of draining fistulae, was based on the investigators' physical evaluation of the patient; a fistula was considered to be closed when it no longer drained, despite gentle finger compression.^{11,12,17} Patients were assessed for fistula closure at weeks 4 and 8. At each visit, the CDAI¹⁸ and PDAI¹⁹ scores were also determined. C-reactive protein (CRP), adverse events, and concomitant medications were assessed at each time point.

Response was defined as a 50% or more reduction in the number of draining fistulae at weeks 4 and 8. Patients not exhibiting response until week 8 were termed late responders. Relapse was defined as an increase by 1 or more in the number of draining fistulae for 2 sequential visits compared with the number present at time of response.

Statistical Methods

The primary data analysis set for efficacy was the intent-to-treat population and included all patients who were randomized to treatment. The population for the safety analyses consisted of all patients who received at least 1 dose of study medication.

The primary efficacy endpoint was the proportion of patients achieving treatment success, defined as a reduction of at least 50% in the number of draining fistulae during blinded treatment at both week 4 and week 8. Patients who either discontinued or who met treatment failure criteria before week 8 were not considered treatment successes. Late responders were also not considered to have met the primary efficacy endpoint. For the analysis of the primary endpoint, the proportion of patients in each treatment arm was compared using Fisher's exact test for treatment group differences.

Secondary efficacy endpoints included the proportion of patients with complete response, defined as 100% nondraining fistulae at both week 4 and week 8, fistula response at week 8,

and change in CDAI scores from baseline over 8 weeks of treatment. Late responders were not considered as having met the primary endpoint and were therefore analyzed separately. Secondary response endpoints and adverse events were compared between treatment groups using Fisher's exact test. Changes in CDAI score from baseline and other continuous variables were tested using repeated measures analysis of variance analysis. The primary safety endpoint was the incidence of treatment-related adverse events over 24 weeks of treatment. Safety data from the initial 8 weeks of treatment and from the alternate blinded treatment phase of the study were pooled for analyses.

It was estimated that 120 patients per treatment group (240 patients overall) would provide 90% power to detect a 20% improvement in treatment success at $\alpha = 0.05$ (two-sided) by use of the Fisher's exact test, assuming a 20% treatment success rate in placebo-treated patients and a 40% treatment success rate in the AST-120 treatment group.

A generalized linear mixed model was used to calculate the odds ratios of treatment success for suggested potential predictors in univariate model and multivariate models. The generalized linear mixed model incorporated random study site effects to account for clustering. The potential predictors with a P value <0.1 in univariate model were included in the multivariate model to assess the statistical significance adjusted for covariates. Age, gender, and treatment group were enforced in the multivariate model. Potential predictors included age, sex, duration of disease, primary location of disease, primary symptom (diarrhea versus others), prior surgical intervention to fistula (yes, no), prior Crohn's treatment (corticosteroids, immunosuppressants, anti-TNF), Crohn's treatment continued (corticosteroids only, immunosuppressants only, corticosteroids plus immunosuppressants), concurrent antidiarrheal medication (yes, no), CDAI (below and above the median), number of draining fistulae (1, 2, >2), CRP (above and below the median), and PDAI (below and above the median).

Ethical Considerations

These trials were designed, conducted, and reported in accordance with the principles of Good Clinical Practice guidelines. Before participating in the trial, patients at each center reviewed and signed an informed-consent document that had been approved by the respective institutional review board.

RESULTS

Patient Disposition and Baseline Characteristics

Two hundred eighty-nine patients were screened, and 249 patients were randomized. One hundred sixty-five patients were enrolled in Europe, 71 patients in North America, and 13 in Israel. The disposition of these patients over the entire 24 weeks of the study is depicted in Figure 2. Of the 122 patients enrolled in the AST-120 group, 110 patients (90.2%) completed 8 weeks of therapy, and 12 patients discontinued treatment before week 8. Of the 127 patients randomized to placebo, 111 (87.4%) completed 8 weeks of therapy, and 16 discontinued before week 8. Three patients in the AST-120 treatment group and 5 in the placebo-treated group discontinued therapy for treatment failure, whereas 4 patients in the

AST-120 treatment group and 6 patients in the placebo group discontinued therapy for adverse events. The primary cause of treatment failure was the need for additional therapies to treat Crohn's disease. Compliance with study medication was 84% in treatment groups.

Demographic and clinical characteristics between both study arms were balanced at baseline, with the exception of a slight predominance of men in the AST-120 (60.6%) versus the placebo (51.2%) group ($P = 0.45$) (Table 1). Mean patient age was 38.0 years with a mean duration of disease of 11.6 years. The mean number of fistulae per patient was 1.6. Six patients had concomitant enterocutaneous fistulae, and 6 patients had coexistent rectovaginal fistulae. Mean CDAI score (149.7 versus 151.5), PDAI score (7.7 versus 7.6), and CRP serum levels (1.44 versus 1.53 mg/dL) were similar between treatment groups (AST-120 versus placebo, respectively). At baseline, CRP was elevated in 46.7% of AST-120 patients and 43.3% of placebo-treated patients. 36.9% of patients had previously used anti-TNF agents. Over 85% of patients had a prior or current use of immunosuppressive agents, and 61.9% had previously used corticosteroids. 53.8% and 23.7% of patients were receiving concomitant immunosuppressive therapy or corticosteroids, respectively, at study baseline, and 15.7% were receiving antibiotics. The use of these agents was equally distributed among treatment groups.

Efficacy

Fistula Response at Week 4 and Week 8—The primary endpoint for the study, the proportion of patients with a reduction from baseline of at least 50% in the number of draining fistulae at both weeks 4 and 8, was not realized in this study. Seventeen (13.9%) patients in the AST-120 treatment group and 21 (16.5%) patients in the placebo met the primary endpoint ($P = 0.60$) (Fig. 3). No differences were noted in the proportion of patients achieving fistula response when the AST-120 and placebo treatment groups were compared at week 4 (23.0% versus 25.2%, $P = 0.77$) and week 8 (27.0 versus 34.6%, $P = 0.22$). There were also no differences noted in the proportion of patients achieving complete response (11.5% versus 11.0%, AST-120 versus placebo, $P = 0.88$) or late response at week 8 (13.1% versus 18.1%, $P = 0.22$). Minimal reductions in CDAI and PDAI scores were noted in both treatment groups at weeks 4 and 8, but no differences were noted between treatment groups, and CRP levels remained unchanged with treatment (Fig. 4). Reductions in the numbers of draining fistulae, abdominal pain scores, and bowel movement frequency were noted at weeks 4 and 8, but differences between treatment groups likewise failed to reach statistical significance.

Univariate and multivariate analyses of baseline variables were performed to identify predictors of treatment success in the combined AST-120 and placebo groups (Table 2). Both a serum concentration of CRP above the median of 0.6 mg/dL and a CDAI score above the median of 151 at baseline were associated with a reduced likelihood of treatment success (odds ratio, 0.40; confidence interval, 0.19–0.87; $P = 0.02$; and odds ratio, 0.45; confidence interval, 0.21–0.97; $P = 0.04$, respectively). None of the other baseline variables tested, including age, sex, duration of disease, primary location of disease, primary symptom, prior surgical intervention, prior Crohn's treatment (anti-TNF, corticosteroids, and/or

immunosuppressants), or concomitant Crohn's treatment (corticosteroids, immunosuppressants, and/or antidiarrheals) achieved significant associations.

Safety

There was an overall incidence of adverse events reported in the AST-120 group similar to the placebo group. During the initial 8 weeks of treatment, 47 (38.5%) of the AST-120 patients and 60 (47.2%) of the placebo patients experienced at least 1 adverse event ($P=0.20$). The highest proportions of adverse events during the initial 8 weeks of treatment were GI (21.7%) and infectious (15.3%; Table 3). The incidence of adverse events in other organ systems was 6% or less. A similar profile of adverse events was noted over the entire 24 weeks of the study.

A total of 18 patients suffered 19 serious adverse events requiring hospitalization; 10 patients treated with AST-120, and 8 with placebo. Six of these events were due to exacerbation of Crohn's disease, 6 due to exacerbations of fistulae or development of abscesses, and 6 due to other causes. Causes of hospitalized events were evenly distributed across 2 treatment groups. Twelve events occurred during the initial 8 weeks of treatment (7 AST-120, 5 placebo) and 6 (3 AST-120, 3 placebo) in the alternate blinded treatment phase of the study. Ten of the 19 events were considered not related to treatment.

An analysis was undertaken to evaluate adverse events related to fistula worsening and fistula-related abscess formation during the initial 8 weeks of treatment. Eight patients in the placebo group reported worsening fistulae symptoms compared with only 1 in the AST-120 group ($P=0.04$). However, 6 patients treated with AST-120 developed abscesses compared with 3 patients treated with placebo. Overall, the incidence of fistula-related adverse events was similar between the 2 groups.

Seven (6.3%) placebo-treated patients experienced worsening abdominal pain compared with only 2 (1.6%) in AST-120-treated patients. This numerical difference favoring AST-120 was not statistically significant ($P=0.17$). The total number of patients experiencing adverse events related to Crohn's disease symptoms (including diarrhea, bowel obstruction, and abdominal pain) was similar between treatment groups, 19 (15.5%) versus 22 (17.5%), AST-120 versus placebo, respectively.

DISCUSSION

This multicenter trial represents the largest prospective trial to date evaluating the effects of a therapeutic agent on fistula drainage in patients with Crohn's disease. Two hundred forty-nine patients were enrolled at 89 investigative sites from 12 countries in North America, Europe, and Israel. Our goal was to replicate the findings of Fukuda et al,¹⁷ which reported the beneficial effects of an 8-week treatment course of AST-120 in a smaller study of 62 Japanese population patients with Crohn's disease fistulae between 2000 and 2002. We failed to confirm a significant benefit of AST-120 over placebo in perianal fistulizing Crohn's disease.

The endpoints employed in the current trial were comparable with those used to demonstrate the efficacy of infliximab in prior studies of fistulizing Crohn's disease.^{11,12} The estimated 20% difference in treatment success rate, defined as a reduction of at least 50% in the number of draining fistulae at weeks 4 and 8 between placebo and AST-120 was not achieved. The fistula response rate with AST-120 of 25.4% at week 8 was, in fact, numerically lower than the 34.6% for the placebo-treated patients. These findings were in contrast with those of Fukuda et al,¹⁷ who reported a 37% of 8-week improvement rate in AST-120 patients versus 10% in patients under placebo. It is noteworthy that the Fukuda study was conducted in a Japanese study population, which could differ in the pathogenesis and natural history of disease from a Western population. The higher placebo response reported in our study is more consistent with the placebo response rate of 26% reported previously in an induction study with infliximab in a Western patient population.¹¹

Another potential explanation for the discrepancy between the findings of Fukuda et al and those of this study could lie in the differences between the demographics of the study populations. Fukuda et al recruited predominantly younger males with a lower BMI. Over two-thirds of their patients were treated with an elemental diet as their primary therapy, for which some evidence for its efficacy for fistula response has been provided by another Japanese study.²⁰ Only 20% of patients in the Fukuda et al study had previously received immunosuppressive agents, and none had received anti-TNF therapies. Less than 20% were still receiving corticosteroids at randomization. Thus, aside from other obvious differences in genetics, diet, and possibly bacterial flora between Japanese and Western patients, their patients were mostly treatment-naïve by current Western standards. In our study, over 80% of the subjects had previously received immunosuppressants and 36.9% had received anti-TNF therapies, predominantly infliximab, and 26.5% and 52.1% of patients were still on corticosteroids and immunosuppressants, respectively, at baseline. Thus, the FFAST-1 patients were a more treatment-experienced population exposed to a more prolonged and wider variety of immunosuppressive agents.

Table 4 compares the population in this study with that of Fukuda et al and other prospective placebo-controlled fistula trials with a primary or secondary endpoint of fistula response. The increasing prevalence of prior immunosuppressive use, comprising 71% in the study population in the Sands trial,¹² and anti-TNF use, which comprised nearly 50% of in the study population of Colombel et al,¹⁰ highlights the changing therapeutic landscape of Crohn's disease in Western treatment centers over the past decade. The patients in this study had generally lower clinical and inflammatory activity, as expressed by CDAI, PDAI, and CRP, than the patients in these earlier trials. Thus, our patients might have had a more chronically fibrotic and less acutely inflamed fibrotic fistula tracts that would be more amenable to surgical therapies than a pharmaceutical intervention. As suggested by the multivariate analysis, these patients may have also been more prone to spontaneous improvement with placebo treatment. An additional explanation for the divergent results could be that the dose of medication used in this population was insufficient to observe a measurable effect. The adsorptive capacity of AST-120 is directly related to the quantity of drug in the GI lumen, and a formal dose-response study had not previously been performed in this indication. The larger body size of Western patients might have rationalized the need of a higher dose than employed in this trial.

As in the Fukuda study, AST-120 in the current trial was well tolerated. We observed an incidence of adverse events, including those related to fistulae, which in the AST-120 group was similar to placebo. This safety experience likely represents the fact that AST-120 is not absorbed and that toxins and bacterial products that adhere to it are passed out inertly in the stool with the drug substance. The high rate of compliance with study medication confirmed the acceptance and tolerability of the sachet formulation in Western populations.

It has been hypothesized that unidentified factors produced by the intestinal flora and dietary components might play a role in the pathogenesis of perianal fistulae.²³ The pharmacologic mechanism of AST-120 has been linked to the adsorption of proinflammatory molecules, such as bacterial toxins, bile salts, and hydrogen sulfide that possess the potential of injuring the mucosal barrier.^{14–16} A recent report from an open-label, uncontrolled U.S. study on the potential benefit of AST-120 in patients with pouchitis after ileal pouch–anal anastomosis would be in line with such mode of action.¹⁶ However, in view of the conflicting results of our study, the therapeutic potential of AST-120 in inflammatory bowel disease remains elusive, although a mechanism for an anti-inflammatory effect has been proposed.²⁴

Data on predictors of fistula response are not available from controlled trials in Crohn's disease. In the combined AST-120 and placebo group, we observed an inverse relationship between fistula response and serum concentrations of CRP and CDAI. This finding seems of relevance for future studies designed to investigate therapeutic efficacy for perianal fistulizing Crohn's disease and for clinical practice because patients with low inflammatory or clinical activity might be more likely to improve spontaneously. This is in line with recent observations from luminal Crohn's disease, where objective signs of inflammation help to select for responders towards biological treatment.²⁵ However, as to whether in our study serum concentration of CRP reflected only local inflammation in the fistula tracts, paralleled luminal inflammation or was the expression of both remains elusive. The fact that the evaluation of intestinal involvement but in particular or imaging of perianal disease was not mandated for inclusion was a potential weakness of the protocol.

In conclusion, in this largest prospective trial to date to evaluate the impact of a therapeutic agent on perianal fistulae in Crohn's disease, AST-120 seems to be safe and well tolerated. However, in contrast to previous positive reports from a Japanese patient population, we could not demonstrate efficacy of AST-120 over placebo in our patients. The divergent outcome between Asian and largely white patients treated for Crohn's disease shows that our global understanding of inflammatory bowel disease is lacking and indicates that further insights into the differences of genetics, diet, gut flora, and patient demographics between populations are needed. Our observation of serum CRP levels and clinical disease activity as predictors of short-term fistula response might assist for clinical routine management and for the design of future clinical trials.

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Author contributions: W. Reinisch and M. S. Harris authored the original manuscript, and S. Travis and S. Hanauer reviewed the manuscript and provided editorial oversight. H. Wang and N. Shawa performed the statistical analyses and advised on statistical content.

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FIGURE 1.

Study schematic representation showing the flow of patients and the treatments administered during successive phases of the trial.

FIGURE 2.

Patient disposition over the 24 weeks of the trial. AE, adverse event; Tx, treatment; F/U, follow-up; ABT, alternate blinded treatment.

FIGURE 3.

Fistula responses at week 4 and 8. The first set of columns represent the proportion of AST-120 and placebo-treated patients achieving the primary endpoint, treatment success, which was a 50% reduction in the number of draining fistulae at both weeks 4 and 8. The middle columns represent response (50% healing) at week 4 alone; and the rightmost column represents the response rates at week 8 alone. Late responder rates at week 8 are shown in the dotted bars.

FIGURE 4.

Mean CDAI and PDAI scores and CRP levels in the AST-120 and placebo-treated patients over the initial 8 weeks of therapy. None of these changes were statistically significant by repeated measures analysis of variance.

TABLE 1

Baseline Demographics and Clinical Characteristics

Characteristics	All Patients (n = 249)	AST-120 (n = 122)	Placebo (n = 127)
Male patients (%)	139 (55.8)	74 (60.6)	65 (51.2)
Age, mean (SD), yr	38.0 (11.7)	37.5 (11.8)	38.5 (11.5)
Race, n (%)			
Caucasian	240 (96.4)	117 (95.9)	123 (96.9)
Non-Caucasian	9 (3.6)	5 (4.1)	4 (3.1)
BMI, mean (SD), kg/m ²	24.5 (5.0)	24.5 (5.1)	24.6 (4.9)
Duration of disease, mean (SD), yr	11.6 (10.1)	12.1 (10.4)	11.0 (9.7)
Current smoker, n (%)	22 (8.8)	12 (9.8)	10 (7.9)
Primary location of Crohn's disease			
Jejunum (%)	2 (0.8)	1 (0.8)	1 (0.8)
Ileum (%)	119 (47.8)	56 (45.9)	63 (49.6)
Right or transverse colon (%)	35 (11.0)	20 (16.4)	15 (11.8)
Left colon or sigmoid (%)	47 (18.9)	25 (20.5)	22 (17.3)
Rectum (%)	48 (19.3)	22 (18.0)	26 (20.5)
No. of fistula (n)			
Mean (SD)	1.6 (1.1)	1.6 (1.1)	1.6 (1.0)
Median (range)	1 (1.7)	1 (1.7)	1 (1.6)
Other fistula			
Enterocutaneous, n (%)	6 (2.4)	4 (3.3)	2 (1.6)
Rectovaginal	6 (2.4)	2 (1.6)	4 (3.1)
CDAI, mean (SD)	150.6 (83.4)	149.7 (77.0)	151.5 (89.4)
PDAI, mean (SD)	7.7 (3.0)	7.7 (3.0)	7.6 (3.0)
CRP (mg/dL)			
Mean (SD)	1.49 (2.01)	1.44 (1.80)	1.53 (2.19)
Median (range)	0.62 (0.01–11.50)	0.65 (0.01–10.10)	0.59 (0.03–11.50)
CRP ≥ 0.8 mg/dL, n (%)	112 (45.0)	57 (46.7)	55 (43.3)
Concomitant medication, n (%)			
Corticosteroid	59 (23.7)	31 (25.4)	28 (22.0)
Budesonide	9 (3.6)	5 (3.9)	4 (3.1)
Prednisone (or equivalent)			
0–9 mg	11 (4.4)	5 (3.9)	6 (4.7)
10–19 mg	21 (8.4)	10 (7.8)	11 (8.7)
>20 mg	18 (7.2)	11 (9.0)	7 (0.5)
Immunosuppressive agent	134 (53.8)	70 (57.4)	64 (50.4)
Azathioprine or 6-MP	128 (51.4)	66 (54.0)	62 (48.8)
Methotrexate	5 (2.0)	3 (2.5)	2 (1.6)
Other	1 (0.4)	1 (0.8)	0 (0.0)
5-aminosalicylate	117 (47.0)	58 (47.5)	59 (46.5)
Antibiotics	39 (15.7)	24 (19.7)	15 (10.2)

Characteristics	All Patients (n = 249)	AST-120 (n = 122)	Placebo (n = 127)
Antidiarrheals	20 (8.0)	9 (7.4)	11 (8.7)
History of prior or concurrent use, n (%)			
Corticosteroid	153 (61.9)	78 (63.9)	75 (59.1)
Immunosuppressive agent			
Azathioprine or 6-MP	204 (82.5)	106 (86.9)	98 (77.2)
Methotrexate	23 (9.3)	11 (9.0)	12 (9.4)
Other	10 (4.0)	7 (5.7)	3 (2.4)
Previous exposure to anti-TNF agent	92 (36.9)	51 (41.8)	41 (32.2)
Prior surgical procedures			
Seton placement	53 (21.3)	22 (18.0)	31 (24.4)
Fistula incision, drainage or excision	139 (55.8)	65 (53.3)	74 (58.6)
Intestinal resection	59 (23.7)	29 (23.8)	30 (23.6)

BMI, body mass index (weight/body surface area); CRP, C-reactive protein.

TABLE 2

Predictors of Treatment Success from Univariate and Multivariate Model

	Univariate		Multivariate	
	OR (95% CI)	P*	OR (95% CI)	P
Age	1.00 (0.97–1.03)	0.77	1.01 (0.98–1.04)	0.69
Gender, women versus men	0.89 (0.44–1.81)	0.74	0.99 (0.47–2.07)	0.98
Treatment group, AST-120 versus placebo	0.81 (0.40–1.65)	0.56	0.81 (0.40–1.68)	0.57
Duration of disease, ≥15 versus <15 yr	0.51 (0.20–1.29)	0.15		
Primary location of disease				
Small bowel disease	1	—		
Colonic disease	0.57 (0.23–1.38)	0.21		
Rectal involvement	1.31 (0.55–3.10)	0.54		
Primary symptom (with diarrhea versus without diarrhea)	0.71 (0.35–1.44)	0.33		
Prior surgical intervention to fistula: yes versus no	1.06 (0.45–2.52)	0.89		
Prior Crohn's treatment				
Corticosteroids only	1	—		
Immunosuppression only	0.70 (0.21–2.29)	0.55		
Corticosteroids plus immunosuppressants	1.10 (0.42–2.91)	0.84		
Others	0.86 (0.34–2.20)	0.75		
Concurrent antidiarrheal medication, yes versus no	0.36 (0.08–1.67)	0.19		
Total CDAI score, above versus below 151 (the median)	0.39 (0.18–0.83)	0.01	0.45 (0.21–0.97)	0.04
Total PDAI score, above versus below 7 (the median)	0.47 (0.22–1.03)	0.05	0.67 (0.30–1.49)	0.32
No. of draining fistulae				
>2	1	—		
2	2.97 (0.58–15.15)	0.18		
1	3.25 (0.71–14.80)	0.12		
CRP, above versus below 0.6 (the median)	0.35 (0.16–0.75)	0.007	0.40 (0.19–0.87)	0.02

* Adjusted for age, gender, and treatment group. Variables with $P < 0.1$ in the univariate model along with age, gender, and treatment group entered in the multivariate model.

OR, odds ratio; CI, confidence interval.

TABLE 3

Adverse Events, All Causalities, First 8 Weeks (>5% Incidence)

System Organ Class Preferred Term	AST-120 (n = 122) n (%)	Placebo (n = 127) n (%)	Total (n = 249) n (%)
GI disorders	21 (17.2)	22 (26.0)	54 (21.7)
Abdominal pain	2 (1.6)	7 (5.5)	9 (3.6)
Crohn's disease	7 (5.7)	5 (3.9)	12 (4.8)
General disorders/site conditions	7 (5.7)	10 (7.9)	17 (6.8)
Infections and infestations	18 (14.8)	20 (15.7)	38 (15.3)
Musculoskeletal and connective tissue disorders	2 (1.6)	9 (7.1)	11 (4.4)
Nervous system disorders	7 (5.7)	8 (6.3)	15 (6.0)
Skin and subcutaneous tissue disorders	6 (4.9)	9 (7.1)	15 (6.0)

Adverse events, all causalities, observed during the first 8 weeks of study drug administration.

TABLE 4

Comparison of Demographics Across Published Studies

Demographics or Treatment	FHAST-1 (n = 249)	Fukuda et al ¹⁷ (n = 62)	Present et al ¹¹ (n = 94)	Sandborn et al ²¹ (n = 43)	Sands et al ¹² (n = 195)	Colombel et al ¹⁰ (n = 117)	Schreiber et al ²² (n = 55)
Age							
Mean (yr)	38.0	30.1	37.2	39.3	—	37.1	37.4
Median (yr)	38	30	—	—	37	—	—
Gender, male (%)	55.8	82.5	47.0	45.6	51.8	38.2	58.6
Weight (kg)	72.5	59.2	68.6	—	—	70.5	—
BMI (kg/m ²)	25.0	20.9	—	26.1	—	—	—
Disease duration							
Mean (yr)	11.5	—	12.4	—	—	—	9.0
Median (yr)	8.7	—	—	—	11.5	—	7.2
Bowel frequency (n/d)	2.34	3.48	—	—	—	—	—
CDAI							
Mean	151	179	187	170	—	313	310
Median	134	—	173	—	180*	—	—
PDAI							
Mean	7.7	9.2	—	—	—	—	—
Median	7.0	—	9.0	—	—	—	—
CRP (mg/L)							
Mean	1.49	1.55	—	—	—	2.30	—
Median	0.62	—	—	—	0.7	0.9	—
Concurrent treatments (%)							
Elemental diet	0.0	68.4	0.0	0.0	0.0	0.0	0.0
Immunosuppressive agents	52.1	0.0	—	58.7	34.0	46.7	51.7
Corticosteroids	26.5	19.3	—	19.5	36.0	44.0	19.2
Prior therapies (%)							
Anti-TNF	36.9	0.0	0.0	63.0	0.0	49.6	37.9
Immunosuppressives	81.9	20.0	40.0	—	71.0	—	—
Corticosteroids	61.4	—	35.0	—	—	—	—
Fistula endpoint							

Denographics or Treatment	FHAST-1 (n = 249)	Fukuda et al ¹⁷ (n = 62)	Present et al ¹¹ (n = 94)	Sandborn et al ²¹ (n = 43)	Sands et al ¹² (n = 195)	Colombel et al ¹⁰ (n = 117)	Schreiber et al ²² (n = 55)
Primary or secondary	Primary	Primary	Primary	Primary	Primary	Secondary	Secondary
Acute or maintenance	Acute	Acute	Acute	Acute	Maintenance	Acute	Acute

— indicates not reported.

* Estimated.